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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,932	07/29/2002	Frank Luyten	50304/027001	1230

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

WOOD, AMANDA P

ART UNIT	PAPER NUMBER
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1657

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/089,932

Applicant(s)

LUYTEN ET AL.

Examiner

Amanda P. Wood

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-36, 43-45, 51 and 55-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-36, 43-45, 51, and 55-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response and amendments filed 24 January 2007 have been received and entered.

Claims 31-36, 43-45, 51, and 55-60 have been examined on the merits.

Response to Arguments

Applicant's arguments with respect to claims 31-36, 43-45, 51, and 55-59 have been considered but are moot in view of the new ground(s) of rejection.

Specification

The disclosure is objected to because of the following informalities: On page 20, line 6, Applicant recites an amino acid sequence for FGFR-3. Applicant must reference the SEQ ID NO for this sequence in the specification rather than the sequence itself.

Appropriate correction is required.

Claim Objections

Claim 31 is objected to because of the following informalities: In lines 3-5, step 1 of Claim 31 recites the phrase "determining the expression by said cells of a positive marker of chondrocyte phenotypic stability which is BMP-2 and/or FGFR-3 and/or a marker co-detectable with these markers." Step 1 and step 2 clearly indicate that it is optional whether to determine more than one of the positive markers by use of the phrase "and/or." In lines 16-17, step f) of Claim 31 recites the phrase "identifying a

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marker which is co-expressed with said positive markers". The use of the phrase "and/or" in the first part of step 1 and in step 2 is inconsistent with step f), because step f) requires identification of more than one marker, whereas step 1 and step 2 indicate that it is optional whether to determine more than one of the recited positive markers. Appropriate correction is required.

Claim 32 is objected to because of the following informalities: In lines 3-5, step 1 of Claim 32 recites the phrase "determining that activin-like kinase-1 (ALK-1) is not expressed by said cells, and/or a marker is not expressed by said cells which is a marker co-detectable with said ALK-1 marker." Step 1 and step 2 clearly indicate that it is optional whether to determine more than one of the markers by use of the phrase "and/or." In lines 16-17, step f) of Claim 32 recites the phrase "identifying a marker which is co-expressed with said negative molecular marker". The use of the phrase "and/or" in the first part of step 1 and in step 2 is inconsistent with step f), because step f) requires identification of more than one marker, whereas step 1 and step 2 indicate that it is optional whether to determine more than one of the recited negative markers. Appropriate correction is required.

Claim 60 is objected to because of the following informalities: In line 2, the phrase "further comprising" appears twice, presumably in error. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-36, 43-45, 51, and 55-60 stand provisionally rejected on the ground of nonstatutory double patenting over claims 3-15, 27, 30, and 33 of copending Application No. 10/422,475. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method for identifying cells having chondrocyte phenotypic stability comprising assaying the cells for expression of positive and/or negative markers of phenotypic stability, detecting the

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expression of the markers by sets of DNA probes, and therapeutic compositions comprising cells identified by the claimed assay method.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Response to Arguments

Applicant made no arguments regarding the Obviousness-type Double patenting rejection of record, but Applicant did acknowledge the rejection and agreed to address it upon the indication of otherwise allowable subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-36, 43-45, 51, and 55-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for type 2 collagen as a marker which is co-expressed with FGFR-3, does not reasonably provide enablement for any other markers which may be co-expressed with all positive markers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with

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these claims. In particular, Applicant does not demonstrate any other markers which could be co-expressed with FGFR-3, other than type 2 collagen, (see, for example, pg. 30 of the instant specification, Example 9). Applicant describes the only other positive marker mentioned in the specification, BMP-2, as an unrelated "independent positive marker," whereas type 2 collagen, which is also described as independent and unrelated, is actually demonstrated to be co-expressed with FGFR-3 in isolated human articular cartilage cells. Applicant has not provided one of skill in the art with enough information about other markers that may be co-expressed with the positive markers BMP-2, FGFR-3, or type 2 collagen to avoid undue experimentation. Therefore, Applicant is only enabled for identification of type 2 collagen co-expressed with FGFR-3.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, Applicant recites the phrase "identifying a marker which is co-expressed with said negative molecular marker" in lines 16-17 of claim 32. The instant specification does not provide any markers which could be considered as "co-expressed with" the negative markers ALK-1 and collagen type X. Applicant illustrates that "with co-expression, in the context of the present invention, is meant that a second factor or marker is expressed or detectable whenever a first factor or marker is expressed or detectable. For example, whenever...ALK-1 or collagen type X are expressed and detectable." Furthermore, Applicant says that "such co-expressed or co-detectable

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factor[s] or marker[s] can be a recognizable cell surface marker, detectable via polyclonal or monoclonal antibodies and/or specific ligands" (see, for example, pg. 12 of the instant specification). Applicant gives no specific examples of what might constitute a marker that would be co-expressed with either ALK-1 or collagen type X. Any number of different cell surface markers could possibly be considered as "co-expressed" with either of these two negative markers and therefore it would take an undue amount of experimentation for one of ordinary skill in the art to determine what would be such a marker.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-36, 43-45, 51, and 55-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, in Claim 31, lines 16-17, Applicant recites the phrase "identifying a marker which is co-expressed with said positive markers linked to formation of stable, non-vascularized cartilage in vivo." It is unclear what Applicant means by this phrase (i.e., are the markers that are co-expressed with positive markers the same as, or different from, markers that are co-detectable with positive markers, what constitutes a co-expressed marker, and is said co-expressed marker co-expressed only with particular positive markers, such as type 2

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collagen co-expressed with FGFR-3, etc.?). It is unclear whether the markers recited in lines 4-5 and 19-20 (i.e., BMP-2 and/or FGFR-3 and/or a marker co-detectable with these markers) that are recited in the alternative form are intended to be the same markers as that recited in step f), wherein a "co-expressed marker" is recited. The confusion rests in the fact that Applicant recites determination of the markers initially in the optional form (and/or), whereas, in step f), Applicant requires that a second marker that is co-expressed with a positive marker is identified. It would appear from the teachings of Yayon et al (WO 96/41620) that the marker FGFR-3 (a positive marker, as taught in the instant specification) is indicative of mesenchymal skeletal progenitor cells, which can differentiate into bone and/or cartilage, and therefore, that FGFR-3 would be insufficient as a positive marker by itself to indicate cells having chondrocyte phenotypic stability. Therefore, the teachings of Yayon et al indicate that to differentiate between mesenchymal skeletal progenitor cells, which would have only FGFR-3 expressed, and chondrocytes, one would need to identify markers in addition to FGFR-3 on chondrocytes for identifying cells having chondrocyte phenotypic stability. Therefore, for examination purposes, the Examiner will assume that the instant claims require determination of a first positive marker and then identification of a second marker which is co-expressed with said positive marker.

In particular, in Claim 32, lines 16-17, Applicant recites the phrase "identifying a marker which is co-expressed with said negative molecular marker linked to formation of stable, non-vascularized cartilage." It is unclear what Applicant means by this phrase (i.e., are the markers that are co-expressed with negative markers the same as, or

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different from, markers that are co-detectable with negative markers, what constitutes a co-expressed marker, and is said co-expressed marker co-expressed only with particular negative markers?). It is unclear whether the markers recited in lines 3-5 and 20-21 (i.e., ALK-1 marker and/or said marker co-detectable with said negative marker) that are recited in the alternative form are intended to be the same makers as that recited in step f), wherein a "co-expressed marker" is recited. The confusion rests in the fact that Applicant recites determination of the markers initially in the optional form (and/or), whereas, in step f), Applicant requires that a second marker that is co-expressed with a negative marker is identified.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, second paragraph for the reasons set forth above.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda P. Wood whose telephone number is (571) 272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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CHRISTOPHER R. TATE
PRIMARY EXAMINER